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(54) Title: ORALLY ACTIVE, ANTIMALARIAL, ANTICANCER, ARTEMISININ-DERIVED TRIOXANE DIMERS WITH HIGH SELECTIVITY, STABILITY AND EFFICACY AND METHODS OF MAKING THE SAME

(57) Abstract: In only two steps and in 65% overall yield, natural trioxane artemisinin (I) was converted on gram scale into C-10-carba trioxane dimer (3). This new, very stable dimer was then transformed easily in one additional step into four different dimers (4-7). Alcohol and diol dimers (4 and 5) and ketone dimer (7) are 10 times more antimalarially potent *in vitro* than artemisinin (I), and alcohol and diol dimers (4 and 5) are strongly inhibitory but not cytotoxic toward several human cancer cell lines. Water-soluble carboxylic acid derivatives (8a-10c and 12) were easily prepared from dimers (4-6); they are thermally stable even at 60°C for 24 hours, are more orally efficacious as antimalarials than either artelinic acid or sodium artesunate, and have potent and selective anticancer activities. Further derivitization of the alcohol dimers (4 and 17), diol dimer (5) and ketone (7) has produced a number of analogs also antimalarially active *in vitro* at sub-nanomolar concentrations (most notably: pyridine N-oxides (13, 15, 18, 23, 24 and 25), phosphoric acid triesters (26 and 27), sulfonamide (40) and cyclic carbonate (41)). In addition, dimers (13 and 19) are more efficacious (when administered both orally and i.v.) and less toxic (when administered intraperitoneally to mice as a single dose) than clinically-used sodium artesunate, thereby giving them a better antimalarial therapeutic index than sodium artesunate.